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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,064	02/13/2006	Kamalakar Talasila	GEN 3.3-015	4267

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EXAMINER	
CHANG, CELIA C	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
04/23/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patpros@drreddys.com

Office Action Summary	Application No.	Applicant(s)	
	10/510,064	TALASILA ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of group III in the reply filed on Jan. 6, 2009 is acknowledged. The traversal is on the grounds that the claims are not drawn in the traditional Markush grouping language thus should not be made with rule 371 standard. This is not found persuasive because even though the Markush elements were not separately listed in the generic claims, the term "antihistamine" and the term "decongestant" are Markush terms using generic "class" term which is tantamount to an antihistaminic compound selected from the group consisting of "novel polymorph of Fexofenadine, Loratadine, Terfenadine, Cetrizine or a pharmaceutically acceptable salts thereof", or "a decongestant selected from Pseudoephedrine, phenylephrine, phenylpropanolamine or a pharmaceutically acceptable salts thereof" etc. Therefore, the Markush practice is proper. Applicants' generic inclusion of all the same subject matter in the three groups as presented on page 5 is erroneous. Please note that in each grouping of the Markush elements, the subject are "mutually exclusive" and not overlapping, for example group III does not contain fexofenadine form X and pseudophedrine salt.

The requirement is still deemed proper and is therefore made FINAL.

The delineated election falls within group I wherein the antihistamine is fexofenadine hydrochloride form X with cellulose, mannitol, starch and croscarmellose, and the decongestant is a salt of pseudoephedrine and polyvinylacetate and povidone, thus, drawn to group I.

Claims 1-17 have been canceled. Claim 37 is prosecuted. Claims 18-36 reading on the elected subject matter can be prosecuted together with the election. The remaining subject matter wherein antihistamine is selected from Fexofenadine (excluding hydrochloride in form X), Loratadine, Terfenadine, Cetrizine or a pharmaceutically acceptable salts thereof, or a decongestant selected from Pseudoephedrine, phenylephrine, phenylpropanolamine are withdrawn from consideration.

2. Claims 37 and 18-36 reading on claim 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a composition containing fexofenadine hydrochloride Form X in a bilayer composition with pseudoephedrine. The maintenance of the "Form X' in a composition depends unpredictably on its process steps. Any step that dissolves the active compound in its crystalline form would not result in a composition that contains such a *form*. It is noted that on page 10, lines 14-17, it was described:

> *"Sift Fexofenadine hydrochloride (Form X/A), mannitol, powaerea ceuulose, crosscarmellose sodium and colloidial silicon dioxide through mesh #20 screen. Sift corn starch iron oxide red through mesh #80 screen. Mix the sifted material in rapid mixer granulator (RMG) for about 25 minutes. Mix the obtained dry mix from RMG with isopropyl alcohol to obtain desired wet mass."*

The mixing with solvent isopropanyl has been recognized in the prior art to dissolve fexofenadine hydrochloride (See US 2005/0256163, p.8, example 7). Dissolution of the crystalline form will result in a composition containing amorphous fexofenadine hydrochloride not the crystalline form X.

To the extend, the dry powder can be directly pressed into tablet, it is noted in per ponderous of art that absent of factual evidence, such compression would result in transformation or disappearing of the crystalline form and a Wand's analysis is made below:

Claims 37 and claims 1-36 reading on claim 37 arerejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as well as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, or was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is well known in the art, at a given pressure and temperature only one thermodynamically stable crystalline form will exist for a given compound (see encyclopedia supra and US Pharmacopia). It is further well recognized in the art that when a crystalline

form for a drug is prepared into a solid formulation, *unless specific and particular* conditions can be described, the "form" is expected to change to the most thermodynamically stable one.

See :

Muzaffar et al. p.60 "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form …." And p.63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism;

Jain et al. p.322-326, manufacturing processes that affect polymorphs ;

Doelker et al. abstract, "One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or the dosage form"

Doelker et al. abstract "…a given drug, although chem. well defined, may exhibits quite different behavior. Process conditions (*grinding, tableting, granulations, drying)* may also affect secondary properties of the drug, such as compactibility, wetttability, soly, dissoln, rate, bioavailability and even pharmacol. activity."

Otsuke et al. p.852 « …in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic *phase transformation* of the bulk CBZ powder during the manufacturing process"

Singhal et al. "..It should be pointed out that a major portion of any formulation effort is the choice of exipients and processes which minimize the chemical instability of the drug…." P.338, left col.

CMU phar. Polymorph. "there are a number of examples in which polymorphic molecules change crystal structure under processing conditions while in contact with liquids or solid material. In these enviroments, it is difficult to apply standard techniques to identify the predict the transformation…." See p.1-2 para.

US 6,627,646, col. 1-2, especially, "..from thermodynamic considerations only one polymorph will be stable;.....however, thermodynamic stability is not sufficient to ensure that the stable polymorph will always be produced…….most transformations occur in suspension and are solvent mediated…..other transformations are irreversible over a broad range of temperature:

The specification provided no description or enablement as to how the crystalline form X can be prepare into a composition which can maintain the particular crystalline structure without the conventional recognized conversion to its thermodynamic form. Per ponderous of evidence in the prior art indicated that for a given polymorph, *absent of factual evidence* the compression

process as disclosed does not *automatically* keeps the original form in the pharmaceutical composition. Absent of this composition, the bilayer composition with "form X" lacks enablement.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 37 and 18-36 reading on 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacLaren et al. US 6,039,974 (recited on 1449) in view of Pharmapedia or Ahjel further in view of Edgren et al. US 6,210,712 and Buhler.

Determination of the scope and content of the prior art (MPEP §2141.01)

MacLaren et al. '974 disclosed bilayer composition containing a layer of antihistamine fexofenadine in immediate release formulation and a layer of pseudoephedrine in sustain release formulation.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and the prior art is that in the immediate release formulation, the election active ingredient (in its dissolved form as explained supra), cellulose, starch and croscamellose sodium have been found (see col. 12 table 1) the other elected ingredient *mannitol* was not employed. Generically, the immediate release layer was describe to be optionally contain diluent such as lactose (see col. 11 lines 25-35). Pharmapedia or Ahjel et al. taught that mannitol and lactose are optional choices of diluent. The difference between the instant elected sustain release layer differ from the prior art in that the instant sustain release layer contains pyrrolidone and vinyl acetate. Pyrrolidone and vinyl acetate sustain release formulation has been conventionally known (see Edgren et al. '712 example 4, pseudoephedrine and pyrrolidon col. 13-14 and generically, the binder is pyrrolidine or optionally mixture of other vinyl monomer including vinyl acetate see col. 6 lines 14-33).

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art in possession of the above references are in possession of the optional choices of diluent or alternative sustain release pseudoephedrine formulation. The picking and choose of an alternative diluent to be prepared into a bilayer system of the prior art with an alternative sustain release layer of conventional prepared composition is prima facie obvious. Because, it is well taught in the prior art that the fexofenadine is prepared in an immediate release formulation and the other layer is a sustain release formulation of pseudoephedrine, in the instant claims, the modification is povidone and vinyl acetate which is motivated by the conventional marketed material for sustain release (see Buhler).

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Apr. 20, 2009

/Celia Chang/
Primary Examiner
Art Unit 1625